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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/822,205	04/09/2004	Hong Zhao	213.1152-CIP	3686

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EXAMINER	
VIVLEMORE, TRACY ANN	
ART UNIT	PAPER NUMBER
1635	
MAIL DATE	DELIVERY MODE
10/01/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/822,205	ZHAO ET AL.	
	Examiner	Art Unit	
	Tracy Vivlemore	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 July 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10 and 12-27* is/are pending in the application.

4a) Of the above claim(s) *20 and 22-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,12-19,21 and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Any rejection or objection not reiterated in this Action is withdrawn.

Election/Restrictions

This application contains claims 20 and 22-26 drawn to an invention nonelected with traverse in the reply filed on January 27, 2006. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claim Objections

Claims 10 and 27 are objected to because of the following informalities:

-claim 10 refers to each X2 being independently selected, however there is only one X2 present in the claimed structure.

-claim 27 recites a structural formula designated as formula (I). Although the structure in claim 27 is a species that falls within Formula (I), the formula itself is different from the Formula (I) already present in claim 1 and should have a different designation.

Appropriate correction is required.

Claim Rejections - 35 USC § 103

Claims 1-10, 12-19, 21 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Teng et al. (US 6,887,906, of record) in view of Greenwald et al. (US 6,303,569, of record) and Dandliker et al. (US 5,707,813, of record).

The claimed invention is directed to prodrug compounds comprising an oligonucleotide and one or more polymers, linking moieties and spacers. In specific embodiments the oligonucleotide component is a phosphorothioate and may be an antisense, the linking moiety comprises an aromatic group, the antisense sequence is SEQ ID NO: 1 and the polymer component is a polyalkylene oxide such as polyethylene glycol.

Teng et al. teach compositions of antisense oligonucleotides useful for therapeutic purposes. One of these is a sequence 18 bases in length targeted to bcl-2 and designated as SEQ ID NO: 34, which is identical to instant SEQ ID NO: 1. At column 10 Teng et al. teach that the antisense compounds of the invention can comprise modified linkages such as phosphorothioates. At column 17, lines 58-67 Teng et al. teach that the oligonucleotides of their invention can be provided in prodrug form, an inactive form that is converted to active form within a cell. Teng et al. do not explicitly teach the use of polymeric prodrugs.

Greenwald et al. teach that poor solubility and rapid degradation *in vivo* are recognized problems of some therapeutic agents. One solution to these problems is the use of prodrugs; inactive forms of a drug that are metabolized within the body to form the active agent. The use of prodrugs can allow one to increase the solubility and

lifetime of a drug. Greenwald et al. teach polymeric prodrugs illustrated at columns 2-3 as formula I. The prodrugs comprise a polymer region, designated as R_{11}, a linker comprising an aromatic group, a spacer designated as L_2 and a drug component designated as B. At columns 18-19 Greenwald et al. teach that the drug component B includes nucleic acids such as DNA or RNA. At columns 9-10 Greenwald et al. teach that polyalkylene oxides such as polyethylene glycol are a preferred polymer component of the prodrug and that these polymers have molecular weights in the range of 2000-100000. The polymer component can have a capping structure such as an alkyl group or can comprise the structure shown as figure II, which would produce a bis-prodrug, wherein the two drug components are identical or different.

It was well known in the art at the time of invention to employ alkyl linkers as a component of an oligonucleotide conjugate. For example Dandliker et al. teach that a commercially available reagent can be used to produce an oligonucleotide having a hexylamine at the 5' terminus. This linker allows the skilled artisan to produce a variety of conjugates by attaching different groups to the oligonucleotide through reaction with the primary amine.

It would have been obvious to one of ordinary skill in the art at the time of invention to produce the bcl-2 sequence of Teng et al. in prodrug form as a polymeric prodrug, including a polymeric bis-prodrug, as taught by Greenwald et al. Teng et al. provide a motivation to make the antisense sequence as a prodrug by explicitly suggesting their oligonucleotides be formulated as prodrugs. Greenwald et al. provide a motivation to make polymeric prodrugs by teaching that polymeric prodrugs allow an

increase in the solubility and stability of therapeutic agents and explicitly suggest their use with nucleic acid drugs. It is further obvious to use hexylamine linkers as a component of the prodrug because Dandliker et al. teach that the person of ordinary skill in the art would be familiar with the use of such linkers due to the commercial availability of reagents that make such linkers and the extensive use of hexylamine linkers for producing a variety of oligonucleotide conjugates. One of ordinary skill in the art would have had a reasonable expectation of success in producing a polymeric prodrug of the bcl-2 sequence because Greenwald et al. provide detailed guidance for the synthesis of polymeric prodrugs.

Thus, the invention of claims 1-10, 12-19, 21 and 27 would have been obvious, as a whole, at the time of invention.

Response to Arguments

Applicants traverse the obviousness rejection by arguing that Teng et al. teach delivery of oligonucleotides using compositions containing fatty acids and/or bile salts as main ingredients and this delivery system is not based on polymeric prodrugs as required by the claimed invention. The examiner acknowledges that Teng et al. do not teach polymeric prodrugs. However, this reference is not relied upon for such a teaching, which is found in the Greenwald et al. reference. Applicants additionally argue that Teng et al. teach prodrugs as SATE derivatives and therefore teaches away from use of polymeric prodrugs. This is not persuasive because the prodrugs taught Teng et al. are not limited to use of SATE derivatives, these derivatives are taught as a

particular embodiment. Since Teng et al. do not discourage use of polymeric prodrugs or state they could not be used, the reference does not teach away from the use of polymeric prodrugs.

Applicants additionally argue that the cited references do not teach the specific conjugation of the claimed elements of polymer, releasable linker (L_1), bifunctional spacer group of 2-10 carbons (L_2), and oligonucleotide. Applicants acknowledge that Greenwald et al. teach polymeric prodrugs yet assert that based on the teachings of the cited references those in the art are left to try to prepare indeterminate linkage combinations of polymeric prodrugs and non-polymeric prodrugs. Applicants further the cited references do not teach the specific linkage of the releasable linker and the 2-10 carbon bifunctional spacer between a polymer and an oligonucleotide and conclude that the person of ordinary skill would have had no reasonable expectation of success in preparing the polymeric prodrugs having the elements recited in the claims

These arguments are unpersuasive because contrary to applicants' assertions, Greenwald et al. do teach the claimed configuration of elements. As stated in the rejection, Greenwald et al. teach at columns 2-3 a prodrug comprising a polymer region designated as R_{11}, a linker comprising an aromatic group (which is equivalent to L_1 of the instant claims), a spacer designated as L_2 (which is equivalent to L_2 of the instant claims) and a drug component designated as B (which can be an oligonucleotide). Greenwald et al. further define L_2 at column 3 as spacers containing more than 2 carbons. Since Greenwald et al. explicitly teach polymeric prodrugs with the components found in the claims and further define L_2 to be a spacer group that

comprises 2-10 carbons, those in the art are not left to try to prepare indeterminate linkage combinations of polymeric prodrugs and non-polymeric prodrugs, all that is needed to produce the claimed compounds is found in the cited references and could be combined with reasonable expectation of success to form the claimed compounds.

With regard to applicants' argument that the rejection is based on hindsight, as noted in MPEP 2145, any obviousness rejection is in a sense necessarily a reconstruction based on hindsight reasoning and is not improper if it takes into account only knowledge within the level of ordinary skill in the art at the time the claimed invention was made. Applicants have provided no evidence that the rejection is not based on knowledge available to those of ordinary skill in the art.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz, can be reached on 571-272-0763. The central FAX Number is 571-273-8300.

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